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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,708	07/06/2001	Keith D. Allen	R-733	3959

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,708	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on *03 February 2003* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *11-16 and 29-46* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 11-16, 29-46 are pending in the application.

Claims 1-10, 17-28 are cancelled. Claims 11-16 and 29-34 are withdrawn from consideration for being directed to non-elected subject matter. Claims 35-46 are currently under examination.

This Office Action is in response to the Amendment filed on 2/3/03.

Response to Amendment

The rejection of claims 8-10 and 17-28 under 35 U.S.C. 112 1st paragraph is moot in light of Applicants' cancellation of the claims.

The rejection of claims 1-4, 9, 10 and 28 under 35 U.S.C. 112 2nd paragraph is moot in light of Applicants' cancellation of the claims.

The rejection of claims 1-8 and 10 under 35 U.S.C. 103 (a) is moot in light of Applicants' cancellation of the claims.

The newly added claims 35-46 are rejected under 35 U.S.C. 112 1st paragraph (scope of enablement) for reasons discussed below.

The newly added claim 40 is rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

The newly added claims 42-46 are rejected under 35 U.S.C.103 (a) for reasons discussed below.

New Grounds of Rejection Necessitated by Applicants' Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous intestinal alkaline phosphatase gene knockout mouse that **lacks production of functional intestinal alkaline phosphatase protein and exhibits the disclosed phenotype of abnormal activity level**, a method of making said mouse, does not reasonably provide enablement for a transgenic mouse comprising any type of intestinal alkaline phosphatase disruption, and exhibits the phenotype of a nociceptive abnormality. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The newly added claims 35-41 are rejected for same reasons as applied to now cancelled claims 8-10 and 17-28 that set forth of the record mailed on 8/26/03 (see pages 3-5).

The nature of the invention is a transgenic mouse comprising a disruption in the intestinal alkaline phosphatase gene and exhibits phenotype comprising a nociceptive abnormality and abnormal activity level; target construct of intestinal alkaline phosphatase gene and a method of making said transgenic mouse. The specification discloses a method for generating said mouse by homologous recombination using an intestinal alkaline phosphatase-targeting construct (see page 51-54, examples 1). The specification further discloses that the homozygous knockout mice exhibit the phenotype comprising nociceptive abnormality and abnormal activity level as shown by the data presented in Table 1.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic knockout models are influenced by the genetic

background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, col.1 1st paragraph, Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous intestinal alkaline phosphatase knockout mouse comprises a nociceptive abnormality and abnormal activity level. And the phenotype of an intestinal alkaline phosphatase knockout mouse is essential for the use of said mouse.

The specification discloses that the word "disruption" comprises alter or replace a promoter, enhancer, or splice site of a target gene, and can alter the normal gene product by inhibiting its production partially or completely or by enhancing the normal product's activity (see page 6-7, bridging paragraph). However, it is not known in the prior art that such "disruption," would produce the phenotype as disclosed by the specification. The specification only discloses a mouse with two alleles of intestinal alkaline phosphatase gene disrupted by inserting a selection marker, and said mouse exhibits the phenotype comprising a nociceptive abnormality and abnormal activity level. Thus, the phenotype of a transgenic mouse comprising a "disruption," as defined by the specification, in an intestinal alkaline phosphatase gene is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic knockout mice that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. One skilled in the art would have to engage in undue amount of experimentation to make and use the invention commensurate in scope with these claims.

The specification discloses that the homozygous mutant mice display an increase in thermal sensitivity as demonstrated by decreased latency to lick their hindpaw during the hot

plate test. However, the specification only provides such data for two pair of mice. Moreover, one pair of mice display very similar latency (24.68 vs 23.28) to hindpaw licking (see Table 1, last col., 5 and 6th cell). It appears that this phenotype is inconsistent between two pairs of wild type and knockout mice. It is also unclear whether the hot plate test indicates thermal sensitivity, pain sensitivity and/or nociceptive sensitivity. As such, whether the IAP knockout mice exhibit the claimed phenotype of nociceptive disorder, increased pain sensitivity and increased thermal sensitivity is unpredictable. One skilled in the art would have to engage in undue experimentation to make and use the invention commensurate in scope with these claims.

This rejection may be overcome by amending the claims to recite only the transgenic knockout mouse that lacks production of functional intestinal alkaline phosphatase protein and exhibits the phenotype of abnormal activity.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "breeding the chimeric mouse to produce the transgenic" in step (d) renders the claim indefinite because it is unclear what is being produced. Appropriate correction is required.

Claim Rejections - 35 USC § 103

Claims 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Manes et al (1990, Genomics, vol.8: 541-554).

The claims are drawn to an intestinal alkaline phosphatase gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in the intestinal alkaline phosphatase gene. The recitation of "wherein the target construct when...exhibits a nociceptive abnormality or activity level abnormality" defines the intended use of the knockout construct, which does not carry patentable weight.

Mansour et al. teach a strategy for targeted disruption of the hprt and proto-oncogene int-2 in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from hprt and int-2 respectively, and a neo selection marker in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make an intestinal alkaline phosphatase gene target construct and knockout mouse.

Manes et al. teach that alkaline phosphatases are highly ubiquitous enzymes present in most species from bacteria to man, and isozymes of tissue specific alkaline phosphatases share highly homologous organization with each other (see page 541, 1st col. lines 1-3, and 2nd col.,

lines 12-14). Manes et al. also teach that this family of genes represent a system suitable for approaching questions concerning the evolution of tissues specific genes and their restricted expression, the mechanisms underlying genetic polymorphism, as well as the progressive change in the catalytic properties and function of enzymes in the context of an isozyme family (page 551, 2nd col., 3rd paragraph, lines 1-2 through page 552, 1st col., lines 1-5). Manes et al. further teach the cloning of mouse IAP, EAP (tissue specific alkaline phosphatase isozyme family member) gene and provided genomic sequence of these genes (see Figure 1 and 3).

Based on the teaching of Manes et al. that alkaline phosphatase gene family represents a system suitable for studying the evolution of tissue specific genes and their restricted expression, it would have been obvious to one of ordinary skill in the art to knockout the tissues specific IAP to study its function. The ordinary artisan would have been motivated to knockout the expression of the IAP gene in a mouse to study the function of this gene in context of the alkaline phosphatase family, and understanding its structure function relationship in evolutionary process, as suggested by the teaching of Manes et al. Functional analysis of a specific gene by using a knockout mouse model is a common practice at the time of filing. The level of skill in the relevant art is high. Absent evidence to the contrary, one skilled in the art would have reasonable expectation of success to make a IAP knockout construct and transform a murine embryonic stem cell with the target construct by following teachings of Mansour et al. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

This application contains claims 11-16, 29-34 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
April 15, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER